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Hepatitis C infection and risk of diabetes: A systematic review and meta-analysis

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Abstract

Background/aims—Several studies found hepatitis C (HCV) increases risk of Type II diabetes mellitus (DM). However, others found no or only sub-group specific excess risk. We performed meta-analyses to examine whether HCV infection does increase DM risk in comparison to the general population and in other sub-groups with increased liver disease rates including with hepatitis B (HBV).

Methods—We followed standard guidelines for performance of meta-analyses. Two independent investigators identified eligible studies through structured keyword searches in relevant databases including PubMed.

Results—We identified 34 eligible studies. Pooled estimators indicated significant DM risk in HCV-infected cases in comparison to non-infected controls in both retrospective ($OR_{adjusted}$=1.68, 95 percent CI 1.15–2.20) and prospective studies ($HR_{adjusted}$=1.67, 95% CI 1.28–2.06). Excess risk was also observed in comparison to HBV-infected controls ($OR_{adjusted}$=1.80, 95% CI 1.20–1.40) with suggestive excess observed in HCV+/HIV+ cases in comparison to HIV+ controls ($OR_{unadjusted}$=1.82, 95 percent CI 1.27–2.38).

Conclusions—Our finding of excess DM risk with HCV infection in comparison to non-infected controls is strengthened by consistency of results from both prospective and retrospective studies. The excess risk observed in comparison to HBV-infected controls suggests a potential direct viral role in promoting DM risk, but this needs to be further examined.

Keywords

hepatitis C; diabetes mellitus, Type 2; meta-analysis; review, systematic; liver diseases; hepatitis B

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INTRODUCTION

An estimated 3% of the world's population (170+ million persons) are infected with the hepatitis C virus (HCV), 55–80% with chronic infection(1). HCV is a significant cause of global morbidity and mortality, responsible for approximately 25% of both chronic liver disease (CLD) and hepatocellular carcinoma (HCC).

HCV infection has also been convincingly linked to several extra-hepatic manifestations including essential mixed cryoglobulinemia, glomeronephritis, and porphyria cutanea tarda (2). Based on early clinical observation, type II diabetes mellitus (DM) was suggested to be another potential extrahepatic manifestation of HCV infection, with excess risk postulated to be due to either direct viral involvement or secondary to HCV-induced liver damage. However, even a small increase in DM risk in HCV-infected patients may be clinically important, as available pharamcotherapies for HCV are less effective with concomitant DM(3) and progression of liver disease has been shown to be worsened(4).

A number of epidemiologic studies have demonstrated significant excess DM risk with HCV infection.(5–15),(16–18) However, others found no significant excess risk(19–26) or excess risk limited to specific segments of the population(27–31). Differences in source of controls, case definition, sample size and underlying target population may explain much of this observed variability among studies. Several general narrative reviews have examined the association between HCV infection and DM. However, they have typically been limited in scope or non-systematic(32,33). The only published meta-analysis examined the association between HCV and DM in a highly limited sub-population of kidney transplant recipients(34).

Our primary goal was, therefore, to conduct meta-analyses to assess whether HCV infection conveys excess DM risk compared to that observed in the general population. We aimed to quantify and appropriately qualify any observed excess risk, to identify any high-risk sub-groups, and to explore potential sources of between-study heterogeneity. A secondary goal was examining DM risk with HCV infection in comparison to that observed in other sub-groups at risk of CLD, including those mono-infected with HBV or HIV. In addition to providing a greater understanding about the association between HCV and DM risk, the findings of these meta-analyses may also help inform clinical practice guidelines and suggest gaps in current understanding that may be important to address in future research.

METHODS

Eligibility Criteria

We followed published guidelines for the conduct and reporting of meta-analyses(35). All published epidemiologic studies providing, or with data to calculate, an estimate of risk of type II or adult-onset diabetes mellitus (DM) among adults infected with hepatitis C (HCV+) compared to adults without infection (HCV−) or an estimate of risk of HCV among adults with DM compared to adults without DM were considered for possible inclusion in the current meta-analysis. To be eligible, both case and comparison groups (e.g., case-control and cross-sectional studies) or exposed and unexposed groups (e.g., cohort study) had to come from the same geographically- and temporally-defined underlying population. To help assure quality and comparability of data from included studies, we further required: 1) publication as an original, peer-reviewed manuscript, and 2) minimum sample size of 200, with at least 100 cases and 100 controls, or 100 exposed and 100 unexposed.

Studies were excluded if they: included children, post-transplant recipients, dialysis patients, pregnant women, or thalassemia or cancer cases; lacked adequately defined case or comparator groups including those where type II DM could not be distinguished from sub-clinical

hyperglycemia or where HCV could not be excluded from other causes of hepatitis; did not provide risk estimates or data necessary to calculate them; or were not published in English. Additionally, as a critical meta-analysis requirement is statistical independence of observations (36), when multiple overlapping reports were available for a single unique study population, we included only the largest or most recent eligible report.

Search Strategy

To identify all potentially eligible studies, two investigators independently conducted structured searches in selected databases including PubMed, ISI Web of Science, and Google Scholar. Searches included combinations of selected key- and text-words including: 'diabetes', 'diabetes mellitus', 'diabetes mellitus, type II', or 'type II diabetes' and 'hepatitis C', 'hepatitis C virus', 'hepatitis', or 'chronic hepatitis' and '*risk', '*rate', 'case-control', 'cohort', 'clinical trial', 'cross-sectional', 'meta-analysis', 'epidemiology', or 'review'. Searches were updated as of May 31, 2008.

We also reviewed the bibliographies of eligible studies as well as those of relevant review articles to identify additional studies not captured by our database searches.

Data Abstraction

Two investigators independently reviewed all identified titles, abstracts and manuscripts to determine if an individual study was eligible for inclusion in this meta-analysis. Disagreements about eligibility were resolved by consensus with a third reviewer.

Data on study methods and results were entered into a structured database. When there was insufficient information on methods, relevant information from any earlier or smaller reports was used instead. If specific quantitative results were not reported, when possible we used available data to calculate them.

Analysis

Because we did not place limitations on type of epidemiological design, studies reporting such varied risk estimates as odds ratios (OR), hazards ratios (HR) and incidence rate ratios (IRR) were all eligible for inclusion in our meta-analysis. However, as a valid meta-analysis requires comparability of risk estimators, we divided eligible studies into comparable sub-groups before performing meta-analysis.

For studies where the OR was the applicable risk estimator, we used available data to calculate or confirm the unadjusted estimator. When there was a discrepancy between reported and calculated estimates, the calculated estimates were used in all subsidiary analyses.

Heterogeneity across studies was assessed using the I^2 of Higgins and Thompson(37) which quantifies the proportion of total variation attributable to between-study differences or heterogeneity as opposed to random error or chance. An I^2>50% was employed to determine if substantive between-study heterogeneity existed. Our decision to perform fixed effects analysis using the Mantel-Haenzel method, or random effects analysis using the Der Simionian and Laird method(38) was based upon our heterogeneity assessment results. Random effects meta-analysis is the preferred method for calculating pooled estimators when there is substantial between-study heterogeneity. All meta-analyses are presented as forest plots with risk estimates for all individual studies as well as the overall pooled estimator. Shaded figures provided for all individual study estimates have dimension proportional to their weight in calculation of the pooled estimator.

Exploratory meta-regression was performed to evaluate potentially important sources of between-study heterogeneity. Variables evaluated included year of publication, source of controls (hospital/clinic-based or not), and region (North America/Europe vs. other). Consonant with widely accepted minimum sample size for regression analysis(39), we performed meta-regression only when there were ≥10 comparable studies per variable assessed. Variables significant at $p<0.15$ were considered potentially important sources of between-study heterogeneity.

Finally, to help assess validity and reliability of our meta-analyses, we performed an analysis of influence and Egger's test. An analysis of influence describes how robust the pooled estimator is to removal of individual studies, while Egger's test, which assesses whether the relationship between effect size and variance differs between large and small studies, was employed to determine if there was potential small study or publication bias(40).

All analyses were conducted using STATA 9.0 (College Station, Texas, USA).

RESULTS

Searches

We identified 223 potentially eligible reports. Review of abstracts and manuscripts resulted in exclusion of 190 reports (85%). The most frequent reasons for exclusion were: publication in an ineligible format including letters/abstracts or the results provided were not from original research including reviews/editorials (n=66); there was no comparator group or else an ineligible case or comparator group (n=45); it contained data on post-transplant patients (n=37); it had a total sample size of less than 200 and/or fewer than 100 cases/exposed and 100 controls/unexposed (n=26); or it was not published in English (n=14).

Study characteristics

Two(5,10) of the 32(5–18,20–25,27–31,41–47) eligible reports we identified included data from two unique studies. Therefore, 34 unique studies were included in our meta-analysis. Baseline study characteristics are provided in Table 1. Additional information on the definition and identification of DM and HCV in individual studies is reported in Appendix 1.

Half of these studies were performed in the U.S. (n=11) or Italy (n=6) and most reported or had data to calculate an applicable prevalence OR (n=29). (Table 1) Among studies with other risk estimates, four reported HRs(16,29,30,42) and the other an incidence rate ratio (IRR) (20).

Sample size was variable among studies with the smallest having a total sample size of 217 (14) and the largest with over 252,000(18). (Table 1) A majority of studies (n=24) utilized hospital/clinic-based controls. However, only 6 studies employed a matched design with use of pre-specified criteria to match cases to controls(5,6,13,18,24,44).

HCV+ vs. HCV−

Eighteen studies had an estimate of DM risk among individuals with HCV infection in comparison to individuals without infection(5–13,16,18,23,24,28,30,42,46,47). (Table 1) Fifteen had ORs(5–13,23,24,28,30,47), while another three had HRs(16,42,46). Results of meta-analyses stratified by specific type of risk estimate are provided below.

Meta-analysis results for studies with ORs

ORs from 14 eligible studies were pooled. (5,7–13,18,23,24,28,30,47) (Fig 1A) We did not include the single remaining study in our meta-analysis because it was restricted to a very

limited subgroup of HCV+ cases with symptomatic mixed cryoglobulinemia(6). As the study by Mehta et al(28) reported ORs for two unique and non-overlapping age-groups, both were able to be used to calculate the pooled estimator. The Marzouk et al study(47) also provided stratified estimates, but with the sub-groups defined by the presence or absence of viremia. However, as both the viremic and non-viremic sub-groups were compared to the same underlying control group, only one of these overlapping ORs could be included in our calculation of the pooled estimator. We therefore used the estimate for the viremic sub-group, representing the majority of the HCV cases, to calculate the pooled estimator.

The unadjusted OR for DM risk with HCV infection in the 14 included studies ranged between OR=0.67 (95% CI 0.65–0.69)(17) to OR=6.7 (95% CI 3.5–12.8)(12), with statistically significant excess risk reported in 11 studies. (Fig 1A) Because substantial between-study heterogeneity was observed (I^2=73%), we employed a random effects meta-analysis. The pooled OR indicated a two-fold excess DM risk with HCV infection ($OR_{unadjusted}$=2.03, 95 % CI 1.52–2.54). (Fig 1A)

Egger's test indicated significant small study or publication bias (Egger's p<0.001). However, none of the variables assessed with exploratory univariate meta-regression (type of controls, region or year of publication) was identified as a potentially important source of between-study heterogeneity. Additionally, our analysis of influence demonstrated that the unadjusted pooled estimator consistently suggested excess DM risk with HCV infection (data not shown).

Given the finding of significant small study or publication bias, we performed sensitivity analyses to ascertain the effects attributable to the single largest study, which had a total sample size of over 252,000(18), and to the single smallest study, which had total sample size of only 477(23). There was still evidence of this bias with removal of the smallest study ($p_{Egger's}$<0.001) and between-study heterogeneity was slightly increased (I^2=75%) (data not shown). However, there was no longer evidence of small study or publication bias with removal of the largest study ($p_{Egger's}$=0.48), with only a small increase in the associated pooled estimator ($OR_{undjusted}$=1.68, 95 percent CI 1.15–2.20). Further, between-study heterogeneity was demonstrably reduced (I^2=57%) (data not shown).

Only 7 studies also provided an adjusted OR, many with a small to modest attenuation in effect. (Fig 1B) Huang et al(30) reported adjusted estimates for sub-groups defined by their viremia status. However, both the viremic and non-viremic sub-groups were compared to the same underlying control group. We therefore used the OR reported for the viremic sub-group as it represented the majority of the HCV cases (74%).

Substantial between-study heterogeneity was also observed among studies reporting adjusted ORs (I^2=58.1%) necessitating use of a random effects model. (Fig 1B) The pooled adjusted OR demonstrated a significant though modestly reduced excess risk of DM with HCV infection ($OR_{adjusted}$=1.68, 95 percent CI 1.15–2.20). However, the pooled OR was reduced slightly and was no longer significant if we used the ORs reported for the smaller non-viremic sub-groups instead of those for the much larger viremic sub-groups for both the Huang et al(30) and the Marzouk et al (47) studies ($OR_{adjusted}$=1.57, 95 percent CI 0.09–3.05). (data not shown) Although there was again evidence of significant small study or publication bias (p<0.001), this again appears to be explained by the single largest study(18). However, given the limited number of studies, we did not perform meta-regression.

Meta-analysis results for studies reporting HRs

Three studies reported HRs as the measure of association between HCV infection and DM (16,42,46). Two were prospective population-based cohort studies performed in Asian populations(42,46) and the other a case-cohort study based on a sample drawn from the larger

Atherosclerosis Risk in Communities (ARIC) cohort study(16) in the U.S. Total follow-up was variable among studies ranging between seven and eleven years. All three excluded prevalent DM cases at baseline and had serologically-confirmed HCV infection.

Both unadjusted and adjusted HRs were reported by all three studies (Figs 2A and 2B respectively). However, the adjusted estimates reported by Mehta et al(16) were stratified according to an *a priori* -specified DM risk category assigned at baseline. As the resulting high- and low- DM risk sub-groups were each compared to their respective and therefore non-overlapping control sub-groups, both estimates were used to calculate the adjusted pooled estimator.

There was no evidence of substantive between-study heterogeneity when considering either unadjusted or adjusted estimates. We therefore employed fixed effects meta-analysis. Both unadjusted and adjusted pooled estimators demonstrated HCV infection significantly increases risk of developing DM ($HR_{unadjusted}$=1.71, 95% CI 1.36--2.06 and $HR_{adjusted}$=1.67, 95% CI 1.28–2.06). (Figs 2A and 2B respectively) While both studies conducted in Asian populations found excess DM risk with HCV infection even after adjusting for BMI (42, 46), the smaller Mehta study(16) found excess risk only in the sub-group at low risk for DM at baseline, including those of younger age or with lower BMI. (Fig 2B) Results for Egger's test suggested no evidence of publication or small study bias when considering either unadjusted or adjusted HRs ($p_{Egger's}$ =0.30 and $p_{Egger's}$ =0.42 respectively). However, given the small number of studies, we did not perform exploratory meta-regression or an analysis of influence.

HCV+ vs. HBV+

Nine studies assessed DM risk in individuals with HCV infection in comparison to that in individuals with HBV infection(5,10,14,17,21,22,41,44,45) (Table 1) Most (n=5) were conducted in European or North American populations.

All nine reported an unadjusted OR (Fig 3A). Given moderate heterogeneity (I^2=50.2%), we employed a random effects analysis. It indicated an approximately 1.8-fold excess risk of DM among HCV+ in comparison to those HBV+ ($OR_{unadjusted}$=1.75, 95 percent CI 1.24–2.25). (Fig 3A) Only three studies provided adjusted estimates(17,41,44) with all including adjustment for relative degree of liver pathology. Given only modest heterogeneity (I^2<50), we employed a fixed effects analysis. The overall pooled adjusted estimator demonstrated a similarly increased risk of DM ($OR_{adjusted}$=1.80, 95% CI 1.20–1.40). (Fig 3B)

Five studies also provided unadjusted risk estimates stratified according to the degree of liver pathology(10,22,41,44,45). (Appendix 2A and 2B respectively) The unadjusted pooled estimator in the context of chronic hepatitis and in the context of cirrhosis both suggested modest though non-significant excess DM risk with HCV infection [$OR_{chronic\ hepatitis}$ =1.28, 95% CI 0.76–1.79 (Appendix 2A) and $OR_{cirrhosis}$=1.59, 95% CI 0.70–2.49 (Appendix 2B)]. To allow a more direct comparison of DM risk observed in the context of chronic hepatitis versus in the context of cirrhosis, we performed a sensitivity analysis where we removed the single study restricted to cirrhotic cases and controls(44). Its removal resulted in a 74% relative reduction in the pooled estimator for DM risk conveyed by HCV within the context of cirrhosis ($OR_{cirrhosis}$=1.18, 95% CI 0.47–1.89). (data not shown)

Results for Egger's test demonstrated no evidence of small study or publication bias in either our unadjusted or adjusted meta-analyses (p=0.38 or p=0.88) and our analysis of influence demonstrated that the pooled estimator was fairly robust to removal of individual studies. (data not shown) However, as there were fewer than 10 studies, we did not perform meta-regression.

HCV+ CLD vs. other cause CLD

Three studies evaluated whether CLD cases attributable to HCV infection had excess DM risk in comparison to CLD cases attributable to other causes of liver disease (OLD), including alcoholic or cholestatic liver.14,15,27 (Table 2) There was evidence of variable increased DM risk with HCV infection in two studies and in a sub-group in the third. However, as the relative proportion of CLD cases attributable to specific other causes was non-comparable across studies, we did not obtain a pooled estimator.

HCV+/HIV+ vs. HCV−/HIV+

Five studies evaluated whether DM risk was increased in individuals co-infected with HCV and HIV in comparison to individuals mono-infected with HIV(20,25,29,31,43) (Table 2) Reported risk estimates included ORs (n=3 studies), HRs (n=1 study) and IRRs (n=1 study). Four reported both unadjusted as well as adjusted risk estimates(20,29,31,43). DM risk estimates with HCV/HIV co-infection among these four studies were variable with significant increased risk reported in one study(43), non-significant excess in another(20) and a significant increase only in specific sub-groups in the remaining two studies(29,31). (Table 2)

A sufficient number of studies to perform meta-analysis existed only for those reporting ORs (25,31,43). (Table 2) Our fixed effects meta-analysis demonstrated a 1.8-fold excess risk of DM with dual HCV/HIV infection in comparison to HIV mono-infection ($OR_{unadjusted}$=1.82, 95 percent CI 1.27–2.38) with no evidence of small study or publication bias ($p_{Egger's}$=0.63). (data not shown) As only two studies also provided adjusted estimates, we did not perform meta-analysis to obtain an adjusted pooled estimator.

DISCUSSION

This is the first meta-analysis to specifically examine the association between HCV infection and risk of diabetes (DM) in the general population as well as in sub-groups at particularly increased risk of chronic liver disease (CLD) including those with hepatitis B (HBV) or HIV infection, or with other causes of liver disease (OLD) like alcohol-related liver disease. Among 34 eligible studies identified for this review, eighteen (15 retrospective and 3 prospective) evaluated DM risk in HCV-infected cases in comparison to general controls without HCV infection. Our meta-analysis which combined the adjusted odds ratios from these retrospective studies demonstrated an approximately 1.7-fold significant increase in DM risk with HCV infection. Similarly, the overall unadjusted pooled estimator demonstrated a significant 2-fold excess risk. Although there was evidence of potential small study or publication bias among these retrospective studies, this effect appears to be largely explained by the single largest study (18) removal of which did not change the overall trend. Further, none of the other potential sources of between-study heterogeneity examined including geographic region, year of publication, or type of controls were significant ($p>0.15$).

Three prospective studies also evaluated whether HCV infection increases risk of developing type II diabetes(16,42,46). All had serological confirmation of HCV and exclusion of DM at baseline. Results from our meta-analysis pooling adjusted HRs suggested HCV infection conveys an approximately 1.7-fold excess DM risk. Interestingly, essentially the same significant excess risk was observed by pooling the unadjusted HRs. In contrast to retrospective studies which have well-established limitations, long-term longitudinal studies with prospectively collected data such as these are particularly valuable as they establish a temporal relationship between HCV infection and subsequent occurrence of diabetes and help support an argument of a causal association. The significant excess DM risk observed in our meta-analysis of prospective studies ($HR_{adjusted}$=1.67) is also highly consistent with the significant excess risk observed in our meta-analysis of retrospective studies ($OR_{adjusted}$=1.70) and adds

further support of those retrospective results. Taken together, the findings of our combined meta-analyses clearly indicate that chronic HCV infection is associated with a modest but significantly increased risk of developing type 2 diabetes in comparison to uninfected controls.

The reasons why chronic HCV infection would induce type 2 diabetes could be manifold. Several experimental studies have suggested a direct role of the virus in promoting DM risk. Within HCV core-transgenic mice, hepatocyte-associated degradation of the HCV core protein leads to negative interaction with insulin signaling by reducing IRS-1 phosphorylation and downstream signaling by Akt(48) and by promoting IRS-1 and IRS-2 degradation(49). In one study, the virus has also been localized in 39% of pancreatic islets in HCV-infected humans and occurs in approximately 54% of all cells within affected islets. Although there is no evidence of increased apoptosis, these HCV+ islet cells exhibit morphologic changes as well as derangement in glucose-stimulated insulin release (β-cell dysregulation)(50). Other experimental studies have suggested a more indirect role of the virus, or rather that it is host response to the virus that promotes DM risk. For example, hepatic levels of pro-inflammatory cytokine TNF-α are doubled in HCV core-transgenic mice with blockade of TNF-α leading to restored hepatic sensitivity to insulin.(51) However, it has also been suggested that HCV infection promotes DM risk as a tertiary consequence of HCV-induced liver damage. Indeed, it is well-established that advanced cirrhosis induces dysregulation of glycemic control which may result in overt diabetes(52). Some support for such a tertiary mechanism comes from a clinical study demonstrating severe fibrosis is the only independent predictor of insulin resistance (IR) as measured by the surrogate marker the HOMA index in HCV-infected patients (53). However, other studies have shown higher IR in HCV-infected patients irrespective of degree of liver injury(4,27,54) with increases in IR evident even at early fibrosis stages(55).

If it is characteristics specific to HCV infection itself rather than just the tertiary liver damage it generates that induces insulin resistance and increases diabetes (DM) risk in human populations, then it would be expected that the prevalence of diabetes should be higher with chronic HCV, than, for instance, with other causes of chronic liver disease. Nine retrospective studies evaluated this hypothesis with respect to HBV infection(5,10,14,17,21,22,41,44,45). Suggestive evidence in support of this hypothesis came from the 1.7-fold significant excess DM risk conveyed by the unadjusted pooled OR. Only three studies also provided an adjusted estimate, with all three including adjustment for degree of liver pathology(17,41,44). Our pooled adjusted OR demonstrated that HCV infection conveys a significant 1.8-fold excess risk of DM beyond that conveyed by relative degree of liver pathology. Four studies also provided unadjusted risk estimates stratified according to the presence of chronic hepatitis or cirrhosis(10,22,41,45). The unadjusted pooled estimators in the context of cirrhosis and in the context of chronic hepatitis both demonstrated only modest non-significant excess risk of DM. However, given low study power as well as lack of adjustment for other possible confounders, these findings are difficult to interpret. The single study comparing DM risk with HCV-infection to that with chronic liver disease (CLD) attributable to a mixture of other causes including alcohol-related disease(27) demonstrated strong and significant excess risk with HCV infection only in the context of chronic hepatitis. Unfortunately, without individual patient data it is not possible to further clarify the impact of liver injury on the relative risk of diabetes associated with HCV infection, both for fibrosis and necro-inflammatory activity.

An estimated 25–30% of HIV cases in the U.S. and Western Europe are co-infected with HCV (56). Highly active anti-retroviral therapy (HAART) used to treat HIV infection is well-known to increase risk of CLD, with development of hepatotoxicity an important reason why HAART is discontinued(57). However, HAART is still recommended for HCV co-infected treatment candidates, with some data suggesting its use may also lessen HCV-related liver disease progression(57). Five studies included in this review evaluated whether HIV cases co-infected with HCV have increased DM risk in comparison to HIV mono-infected cases(20,25,29,31,

43). A small to modest excess risk of DM with HCV co-infection was generally observed though significance of findings was variable. Only three studies provided comparable unadjusted risk estimators (ORs) that were able to be combined in a pooled estimator (25,31, 43). Two studies included cases and controls prior to initiation of HAART(25,43) while the third study adjusted for use of HAART(31). This unadjusted meta-analysis demonstrated co-infection with HCV conveys a 1.8-fold significant excess risk of DM in comparison to that observed in HIV mono-infected cases. However, as only two studies provided adjusted estimates, we did not obtain an adjusted pooled estimator and our unadjusted meta-analysis finding of excess DM risk among HIV patients co-infected with HCV must be considered as suggestive only.

In evaluating findings from our meta-analyses, it is important to consider the potential impact of confounders of the relationship between HCV infection and occurrence of DM, particularly from such well-established risk factors as BMI. The three available prospective studies that evaluated diabetes risk in comparison to uninfected controls reached different conclusions as to what categories of HCV-infected individuals are at increased risk. Specifically, the two larger prospective cohort studies both demonstrated HCV infection conveys additional DM risk beyond that conveyed by age or BMI(16,42,46). This finding is similar to that observed among all 6 retrospective studies which also included adjustment for these factors(8,9,24,28, 30,47). In contrast, the much smaller American case-cohort study, which included only 15 HCV-infected cases, showed only individuals who were already at increased diabetes risk (mainly overweight individuals older than 50) have an additional DM risk due to HCV infection (16). Although the preponderance of current evidence suggests hepatitis C infection may convey additional DM risk beyond that conveyed by BMI, additional prospective studies are therefore needed to sort out the important aspect of the interaction between HCV infection and other risk factors for diabetes including current and historical obesity.

The present study has several strengths as well as some limitations. We used exhaustive search methods to identify all eligible studies and attempted to increase comparability and quality of included studies by using pre-specified eligibility criteria including publication in a peer-reviewed journal, a minimum total sample size and presence of appropriate as well as adequately identified case and control groups. To help assess the validity and reliability of our findings, we also performed additional quality control analyses including meta-regression and sensitivity analyses in order to identify possible sources of between-study heterogeneity. Further, we systematically investigated the potential for small study or publication bias and the impact of removal of individual studies on the pooled estimator was also assessed.

Our application of rigorous eligibility criteria to assure the internal validity of our findings has also imposed some potential limitations, particularly with respect to the generalizability of our results. First, our restriction to studies performed in adults means we are unable to extrapolate these findings to HCV-infected children. Second, our restriction to articles published in the English language means it is possible that complex interactions between ethnicity, HCV infection and the occurrence of diabetes could have been missed in particular ethnic groups if these findings were published exclusively in non-English language journals. However, only a small minority (6%) of studies reviewed were excluded specifically because they were not published in English. Further, 62% of all included studies were performed in countries where English is not the primary language. Third, we included only studies with a minimum total sample size of 200, with at least 100 exposed or cases and 100 controls or unexposed. We employed this criterion to help mitigate the potential for small study bias given the greater likelihood that small studies in particular will be published if they report significant or interesting results(58). Although less than 12% of studies were specifically excluded due to sample size, it is therefore possible that our reported effect sizes might actually be increased if we had included these smaller studies. Finally, we selected only studies reporting on

prevalence or incidence of overt diabetes. This has the advantage of robust and reproducible clinical definitions of the outcome of interest across studies. However, it can also underestimate the magnitude of the relationship between HCV infection and impaired glucose metabolism.

Other limitations are due to insufficient information provided by the eligible studies themselves. Dose-dependent effects could not be demonstrated because viral load and duration of HCV infection were not typically recorded. Other potentially important viral- (e.g., genotype) or host-related factors (e.g., family history of diabetes and visceral adiposity) could also not be examined. Additional prospective studies are therefore needed to determine what specific combination of viral- and host-related factors explain the observed excess risk of type II DM conveyed by HCV infection.

The findings of this meta-analysis could have important clinical implications. Given the demonstrated increased risk of diabetes conveyed by HCV infection, a strong case can be built for screening for glucose abnormalities in all HCV-infected individuals. Second, these data might provide a better insight into the overall burden of disease in chronic hepatitis C. Indeed, if risk of diabetes increases with the duration of exposure to HCV, then diabetes might become a prominent HCV-induced health problem in some patients like those with a low risk of fibrosis progression (e.g., women contaminated with HCV at a young age). Finally, since some reports have shown that HCV eradication improves insulin sensitivity(3) and reduces the incidence of diabetes(59), a reasonable inference would be that some HCV-infected patients at high risk of diabetes occurrence might benefit from antiviral therapy beyond hepatological reasons. Future work is needed in order to determine if diabetes could be prevented or reversed with successful HCV eradication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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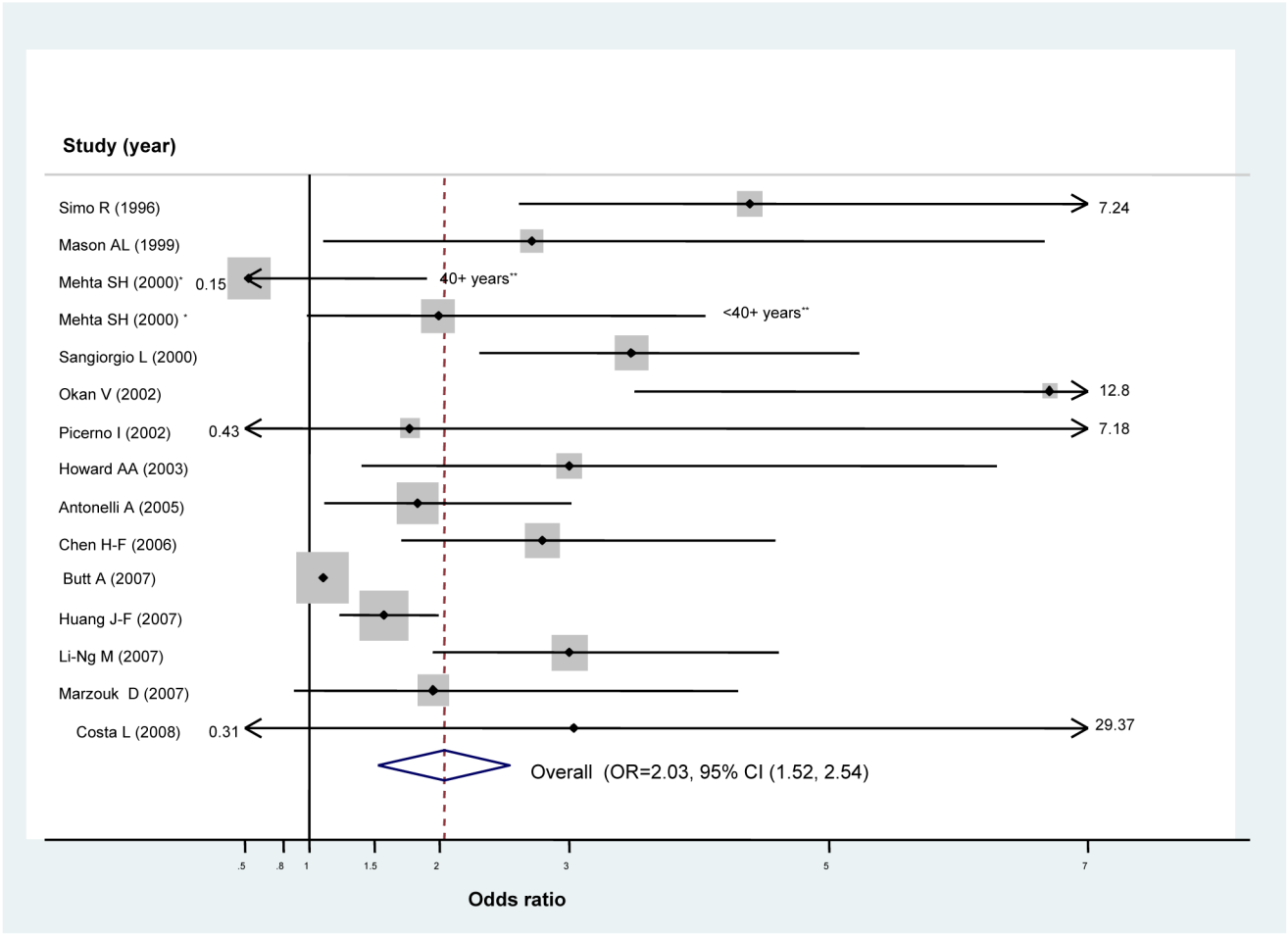
1A. Univariate estimates



*Same publication and same study population

**Non-overlapping estimates (I.e., unique case and comparison group

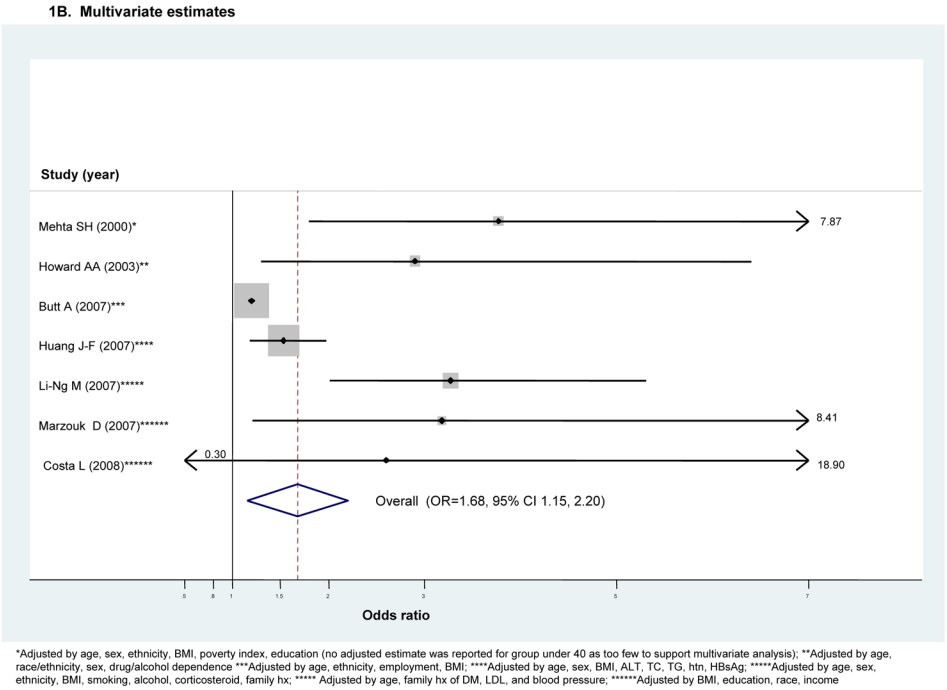
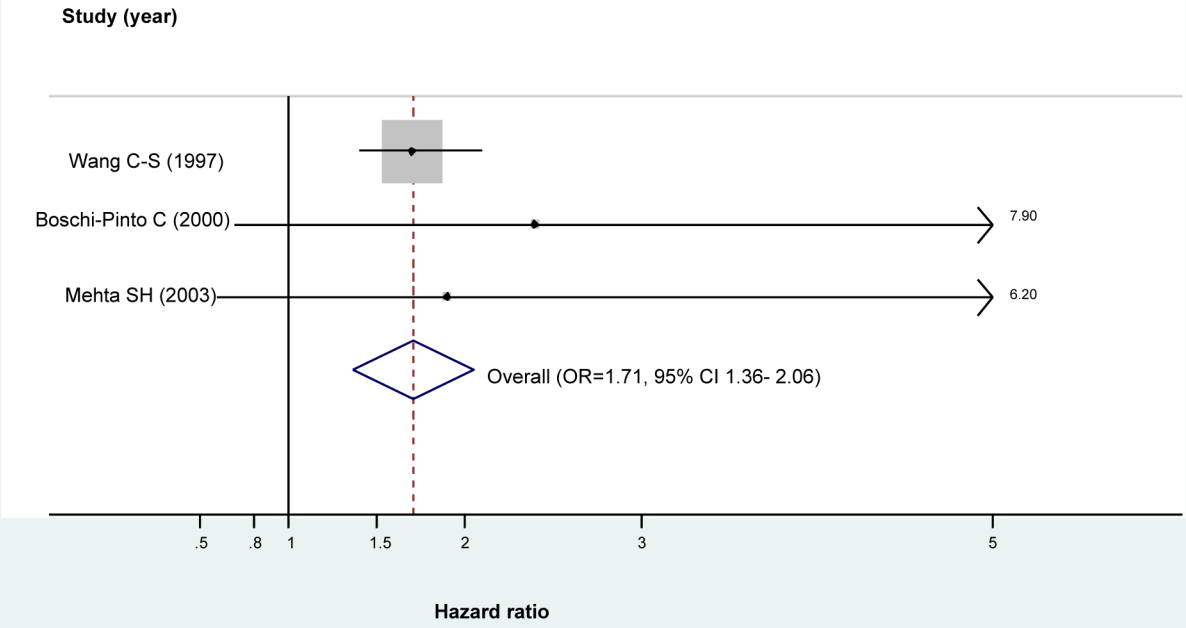


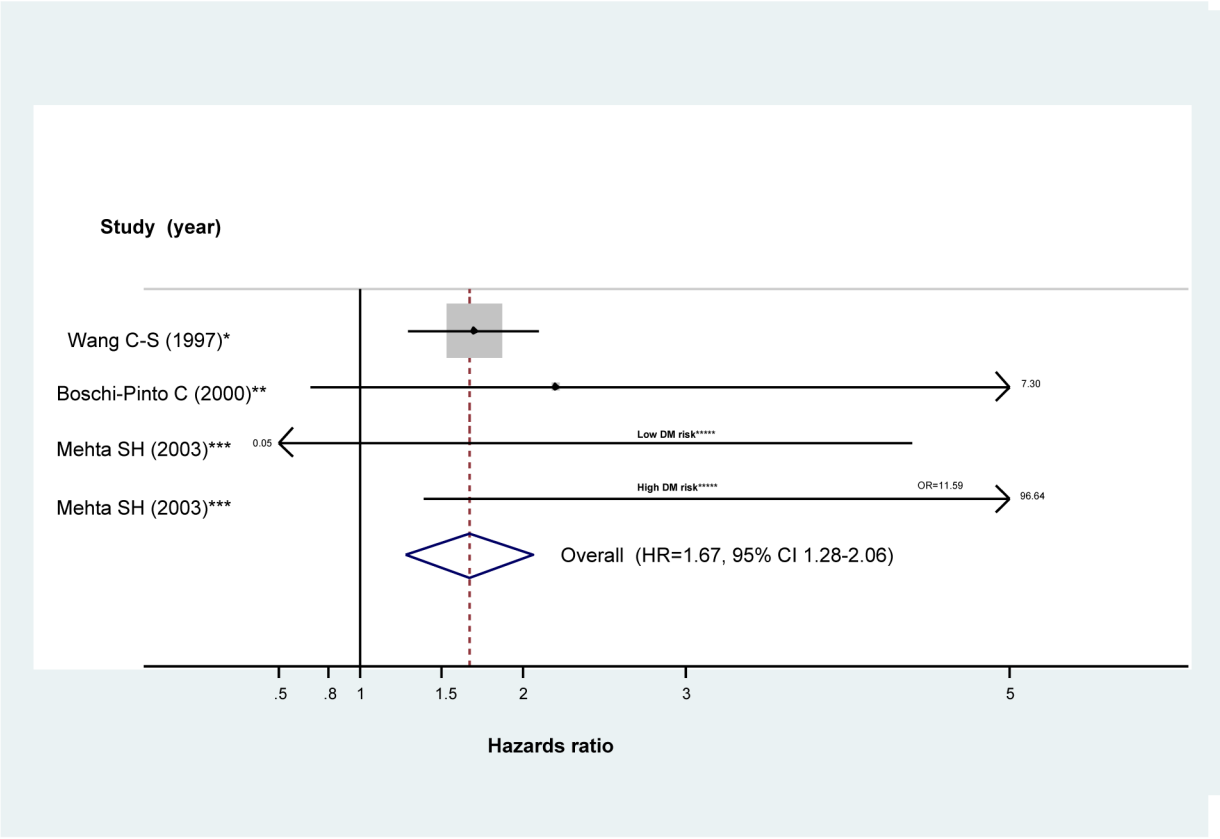
Figure 1. Forest plots for meta-analyses comparing risk of Type II diabetes in HCV infected cases compared to that in non-infected controls in retrospective studies (n=14)^

^Dimension of shaded odds ratio for individual studies is proportional to their total weight in calculation of the pooled estimator.

2A. Univariate estimates



2B. Multivariate estimates

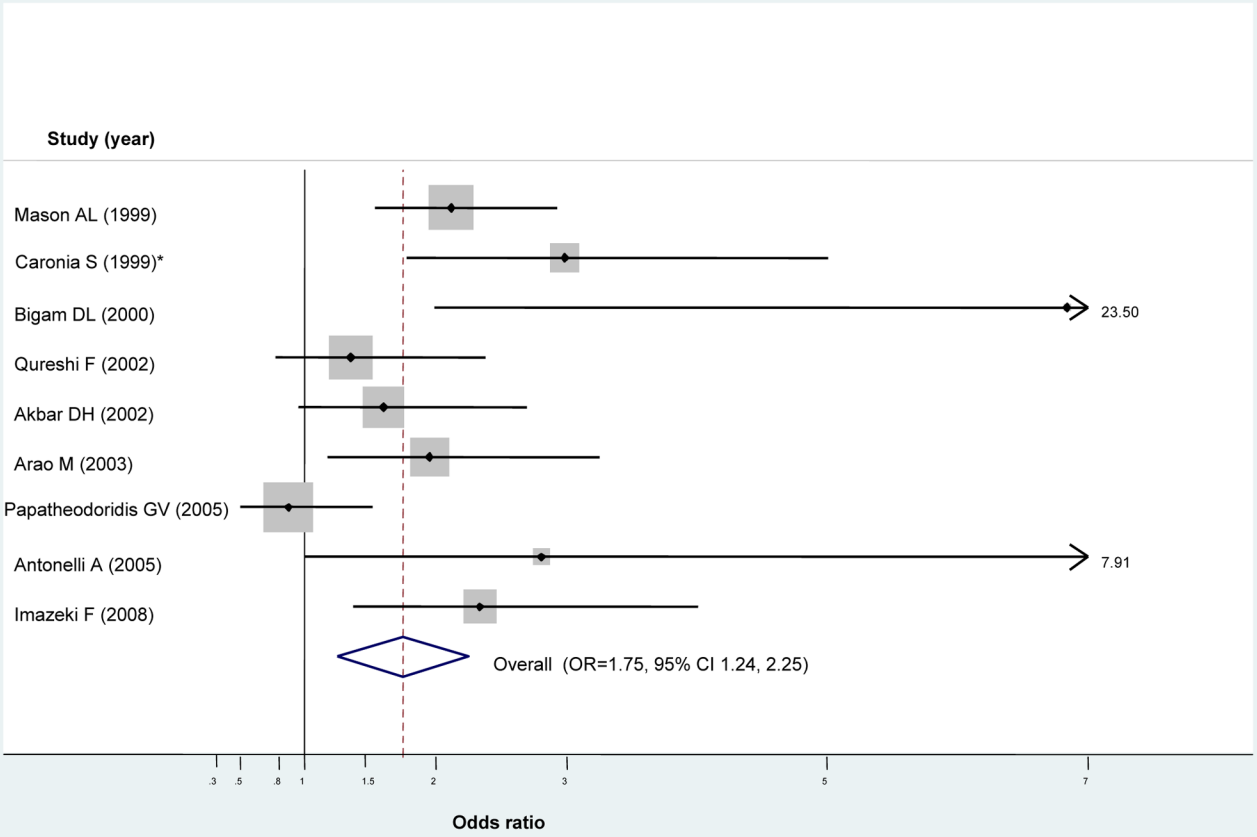


*Adjusted by age, gender, education, obesity, smoking, type infection, alcohol; **Adjusted by age group, sex, drinking, smoking, HTLV-1 status
Same study population, non-overlapping estimates; **'Low risk'-lower BMI and age strata at baseline; *****'High risk' -higher BMI, older age at baseline

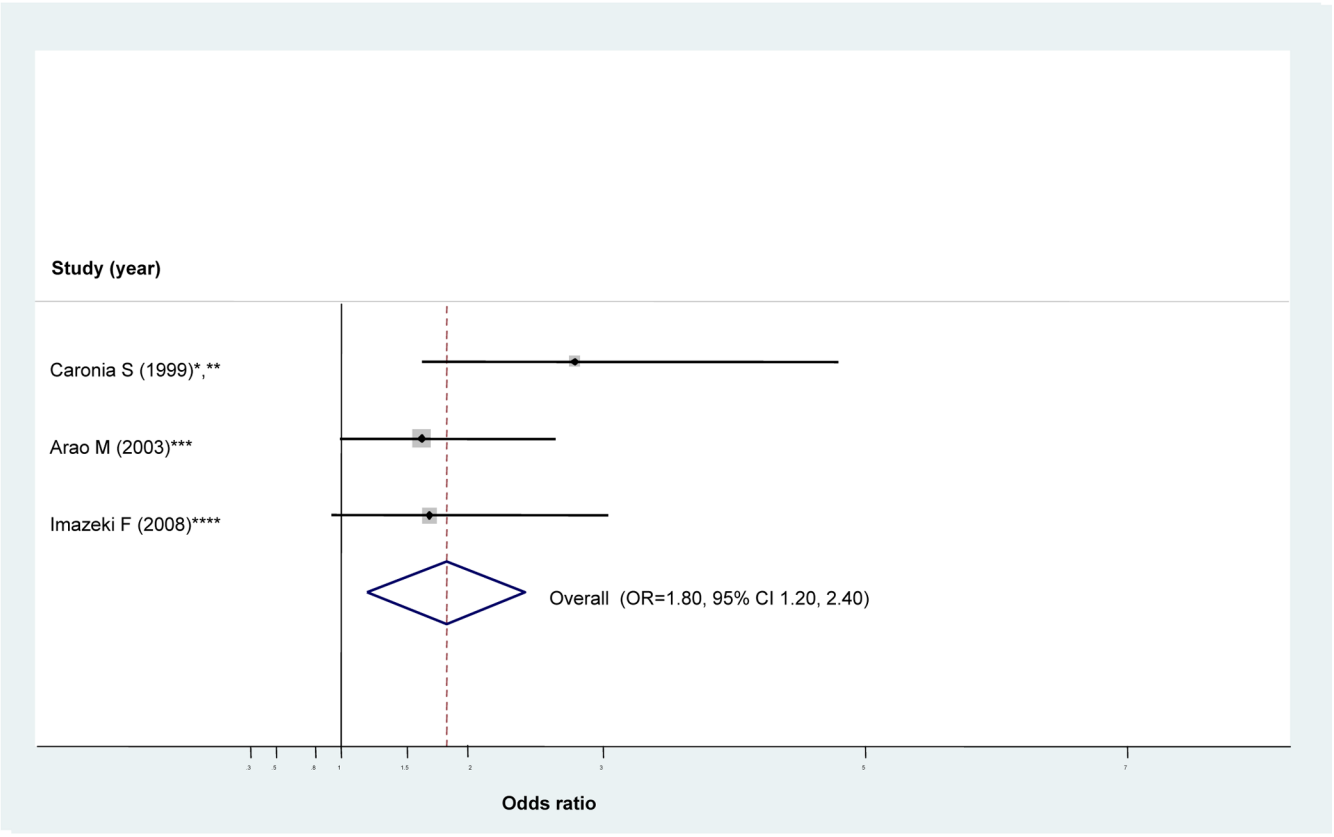
Figure 2. Forest plot of hazard ratios and the overall pooled estimator for longitudinal studies comparing diabetes risk in individuals with HCV infection to that in individuals without HCV infection (n=3)^

^Dimension of shaded hazards ratio for individual studies is proportional to their total weight in calculation of the pooled estimator.

3A. Univariate estimates



*Study restricted to cirrhotic cases and controls



*Adjusted by age, gender, Child-Pugh category
**Study restricted to cases and controls with cirrhosis
***Adjusted by gender, age, cirrhosis, ALT
****Adjusted by gender, age, degree of liver disease

Figure 3. Forest plot for meta-analyses comparing risk of diabetes in HCV-infected cases compared to that in HBV-infected controls (n=8 retrospective studies)^

^Dimension of shaded odds ratio for individual studies is proportional to their total weight in calculation of the pooled estimator.

Table 1

Characteristics of meta-analysis eligible studies examining association between HCV and DM*

Ref #	Name	Year	Country	Study Timing (Measure of Association)	Case or Exposed**	Source of identification	Control or Unexposed***
21	Akbar DH	2002	Saudi Arabia	Retrospective (OR)	HCV+	Hospital	HBV+
6	Antonelli A	2004	Italy	Retrospective (OR)	HCV+ with MC	Hospital	HCV−
5	Antonelli A	2005	Italy	Retrospective (OR)	HCV+ with CLD	Clinic	HBV+ with CLD
5	Antonelli A	2005	Italy	Retrospective (OR)	HCV+ with CLD	Clinic	HCV−
41	Arao M	2003	Japan	Retrospective (OR)	HCV+	Hospital & Clinic	HBV+
14	Bigam DL	2000	Canada	Retrospective (OR)	HCV+ with LF	Hospital	OLD with LF
42	Boschi-Pinto C	2000	Japan	Prospective (HR)	HCV+	Miyazaki cohort study	HCV−
43	Brar I	2007	U.S.	Prospective (HR)	HCV+/HIV+	CPCRA clinical trial	HIV+
29	Butt AA	2004	U.S.	Retrospective (OR)	HCV+/HIV+	VA-HIV+ (1992–2001)	HIV+
44	Caronia S	1999	Italy	Retrospective (OR)	HCV+ with cirrhosis	Hospital	HBV+ with cirrohosis
7	Chen H-F	2006	Taiwan	Retrospective (OR)	DM+	Hospital	DM−
15	El-Zayadi ARM	1998	Egypt	Retrospective (OR)	HCV+ with CLD	Clinic	OLD with CLD
8	Howard AA	2003	U.S.	Retrospective (OR)	HCV+	Methadone clinic	HCV−
30	Huang J-F	2007	Taiwan	Retrospective (OR)	DM+	Kaoshung City cohort study	DM−
31	Jain MK	2007	U.S.	Retrospective (OR)	HCV+/HIV+	Clinic	HIV+
27	Lecube A	2004	Spain	Retrospective (OR)	HCV+	Liver clinic	OLD with CLD
20	Ledergerber B	2007	Switzerland	Prospective (IRR)	HCV+/HIV+	Swiss HIV cohort study	HIV+
9	Li-Ng M	2007	U.S.	Retrospective (OR)	DM+	VA-NY	DM−
47	Marzouk D	2007	Egypt	Retrospective (OR)	HCV+	Zwyat Razin village cohort study	HCV−
10	Mason AL	1999	U.S.	Retrospective (OR)	DM+	Clinics-New Orleans & Baton Rouge	DM−
10	Mason AL	1999	U.S.	Retrospective (OR)	HCV+	VA-St. Louis or Clinic-New Orleans	HBV+
28	Mehta SH	2000	U.S.	Retrospective (OR)	HCV+	NHANES III	HCV−
16	Mehta SH	2003	U.S.	Prospective (HR)	DM+	ARIC cohort study	DM−
12	Okan V	2002	Turkey	Retrospective (OR)	DM+	Hospital	DM−
22	Papatheodoridis GV	2005	Greece	Retrospective (OR)	HCV+ with CLD	Hospital	HBV+ with CLD
23	Picerno I	2002	Italy	Retrospective (OR)	DM+	Hospital	DM−
45	Qureshi F	2002	Pakistan	Retrospective (OR)	HCV+ with CLD	Hospital	HBV+ with CLD

Ref #	Name	Year	Country	Study Timing (Measure of Association)	Case or Exposed**	Source of identification	Control or Unexposed***
11	Sangiorgio L	2000	Italy	Retrospective (OR)	DM+	Hospital	DM−
13	Simo R	1996	Spain	Retrospective (OR)	DM+	Hospital	DM−
18	Butt A	2007	U.S.	Retrospective (OR)	HCV+	VA National Patient Care Database	HCV−
25	Stapleton JT	2007	U.S.	Retrospective (OR)	HCV+/HIV+	ALLHRT cohort study	HIV+
46	Wang C-S	2007	Taiwan	Prospective (HR)	HCV+	A-Lein Township (1997–2003)	HCV−
24	Corrêa da Costa L	2008	Brazil	Retrospective (OR)	DM+	Hospital	DM−
17	Imazeki F	2008	Japan	Retrospective (OR)	HCV+	Hospital	HBV+

Source of identification	Matching factors	Case or Exposed #	Outcome present # (%)	Control or Unexposed #
Hospital	NA	153	35 (21.2%)	226
Population >50 yrs	Age and sex	229	33	217
Clinic	Age	564	71 (12.6%)	82
Population	Age	564	71 (12.6%)	302
Hospital & Clinic	NA	707	148 (20.9%)	159
Hosptial	NA	110	32 (29%)	168
Miyazaki cohort study	NA	222	5 (2.3%)	743
CPCRA clinical trial	NA	436	NR	2,129
VA-HIV+ (1992–2001)	NA	6153	NR	20,835
Hospital	Age and sex	1,151	272 (23.6%)	181
Hospital	NA	820	56 (5.83%)	905
Clinic	NA	591	150 (25.4%)	223
Methadone clinic	NA	418	63 (15%)	139
Kaoshung City cohort study	NA	1,237	96 (7.8%)	8,695
Clinic	NA	388	55 (34%)	1,141
Liver cllinic	NA	498	23 (4.6%)	144
Swiss HIV cohort study	NA	123	31 (25.2%)	6,390
VA-NY	NA	170	61 (35.9%)	331
Zwyat Razin village cohort study	NA	180	9/111 (8.1% viremic), 7/66 (10.6% non-viremic)	577

Source of identification	Matching factors	Case or Exposed #	Outcome present # (%)	Control or Unexposed #
Clinics-New Orleans & Baton Rouge	NA	571	25 (4.2%)	377
VA-St. Louis or Clinic-New Orleans	NA	604	145 (24%)	486
NHANES III	NA	230	NR	9,551
ARIC cohort study	NA	15	7 (46.7%)	1,069
Blood donor registry	NA	692	52 (7.5%)	1,014
Hospital	NA	260	33 (12.7%)	174
Blood donor registry	NA	254	6 (2.4%)	223
Blood bank	NA	302	74 (24.5%)	98
Blood bank	NA	1,514	115 (7.6%)	1,300
Hospital blood donors	Age, sex, previous transfusion, and IV drug use	176	18 (11.5%)	6,172
VA National Patient Care Database	Age, race/ethnicity and sex	126,926	36,047 (14.2%)	126,926
ALLHRT cohort study	NA	160	8 (5%)	1,274
A-Lein Township (1997–2003)	NA	812	116 (24.5%)	3,486
Hospital	Age and sex	206	3 (1.4%)	206
Hospital	NA	544	74 (13.6%)	286

Outcome present # (%)	Male case or exposed # (%)	Male control or unexposed # (%)	Age case or exposed	Age control or unexposed
33 (14.1%)	100 (65.3%)	96 (42.5%)	>40 (67.3%)	>40 (34.1%)
15	58 (25.3%)	217 (23.2%)	67 +/− 12	66+/− 8
4 (4.9%)	181 (32,1%)	30 (36.6%)	61+/−14 (DM+)	67+/− 6 (DM+)
22 (7.3%)	181 (32,1%)	91 (30.1%)	61+/−14 (DM+)	64+/−10 (DM+)
19 (11.9%)	413 (58%)	118 (74%)	40–59 yrs (33%)	40–59 yrs (46%)
8 (4.8%)	71 (65%)	82 (48.9%)	51 +/− 10	48+/− 12 (other CLD), 47+/− 11 (HBV CLD)
6 (0.8%)	89 (40%)	300 (40%)	45–54 yrs (23.0%)	45–54 yrs (24.5%)
NR	77% -overall cohort	NR	NR	NR
NR	NR	NR	<40 35.1% overall cohort	NR
17 (9.4%)	704 (61.2%)	135 (74.6%)	median 59+/−8	median 54+/− 7
23 (2.56%)	428 (52.2%)	503 (55.7%)	56.7 +/− 11.33	53.7 +/− 15.28

Outcome present # (%)	Male case or exposed # (%)	Male control or unexposed # (%)	Age case or exposed	Age control or unexposed
25 (11.2%)	73.3%	76.0%	42 +/− 4	45 +/− 3
11 (8%)	256 (61%)	62 (45%)	<40 (25%)	<40 (55%)
546 (6.3%)	640 (51.7%)	3,652 (42.0%)	57.1 +/− 6.2	54.9 +/− 5.9
333 (24%)	310 (80%)	922 (81%)	40–50 162 (42%)	40–50 309 (27%)
18 (12.5%)	274 (55%)	71 (49%)	52.9 +/− 14.1	54.7 +/− 15.2
1,757 (27.5%)	98 (79.7%)	4,383 (68.6%)	45 (IQR 38–53)	38 (IQR 34–44)
52 (15.7%)	93.3% male overall	NR	58.0 Asian overall, 61.0 PI overall	NR
25 (4.7%)	40.4% male overall	NR	45–54 61 (19.7%) overall	NR
6 (1.6%)	12 (48%) HCV+	309 (54%)	59 +/− 15	62 +/− 14
63 (13%)	386 (64%)	375 (78%)	43–49 yrs n=117 (20%)	43–49 yrs n=74 (19.5%)
NR	49%-overall	NR	40–49 yrs (19%) -overall	NR
541 (50.6%)	5 (62.5%)	NR	44–49 yrs (37.5%)	NR
12 (1.2%)	260 (37.6%)	881 (86.9%)	51.9 yrs	NR
25 (14.4%)	15 (45.5%) DM+	21 (84.0%) DM+	53.9 +/− 11.5 (DM+)	59.4 +/− 10 (DM+)
3 (1.3%)	148 (58.3%)	143 (64.1%)	51.7 +/− 5.8	47.2 +/− 6.1
19 (19.4%)	65.8% male overall	NR	42 +/− 13 years overall	NR
30 (2.3%)	668 (44.1%)	NR	63.1+/−10.5	NR
156 (2.5%)	46.7% (DM+)	43.2% (DM+)	46.4 +/−21.2 (DM+)	48.3 +/− 14.6 (DM−)
33,255 (13.1%)	245,729 (96.8%)	245,729 (96.8%)	51.8	50.8
31 (2%)	130 (81%)	1,032 (81%)	43 median	37 median
300 (8.6)%	382 (47.0%)	1,536 (44.1%)	58.9 +/− 10.7	55.8 +/− 11.5
2 (1.0%)	58 (28%)	58 (28%)	55	54.6
18 (6.3%)	164 (57.3%)	164 (47.2%)	59.6 +/− 13.1	44.5 +/− 13.0

* See also Appendix 1 for other key study characteristics

** Case or exposed dependent on type of design, see also Appendix A for detail on ascertainment

*** Controls or unexposed dependent on type of design, see also Appendix 1 for details on ascertainment

Abbreviations: HCV (hepatitis C virus infection); DM (diabetes mellitus), OLD (other liver disease including alcohol-induced liver disease and chronic hepatitis); NA (not applicable); NR (not reported); MC (mixed cryoglobulinemia); CLD (chronic liver disease); LF (liver failure); ALT (alanine aminotransferase); HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; PI, Pacific Islander

Table 2

DM risk with HCV infection in comparison to that in two high risk sub-groups: HIV-infected or with other causes of liver disease (OLD) [*].

Ref #	Study (year)	Type of Estimator	Stratified by:	Unadjusted Estimate	95% CI	Stratified by:	Adjusted Estimate	95% CI	Adjustment factors:
				HCV+/HIV+ vs. HIV+					
43	Brar (2007)	OR		2.59	(1.63–4.14)		1.91	(1–3.64)	age, BMI, gender, ethnicity, drug use, MSM status, AIDS defining illness
29	Butt (2004)								
			Era			Era			
		HR	HAART	1.98	(1.34–2.92)	HAART	1.39	(1.27–1.53)	age, minority race, alcohol or drug dx, end-stage liver disease present
		HR	pre-HAART	1.23	(1.13–1.33)	pre-HAART	1.01	(0.71–1.36)	age, minority race, alcohol or drug dx, end-stage liver disease present
31	Jain (2007)	OR		1.6	(1.1–2.2)				
				DM risk[**]					
						Low	2.0	(1.2–3.2)	race
						High	1.2	(0.7–2.1)	race
20	Lesgerber (2007)	IRR		0.78	(0.5–1.21)		1.2	(0.63–2.29)	sex, age, mode and stage of infection, ethnicity, CD4 (count/nadir), smoking, BMI, central adiposity, time dependent rx
25	Stapleton (2007)	OR		1.67	(0.92–3.04)				
				HCV+ vs. OLD[*]					
27	Lecube (2004)	OR		1.36	(0.85–2.19)				
			Stage						
			Chronic hepatitis	2.96	(1.24–7.06)				
			Cirrhosis	1.25	(0.63–2.42)				
14	Bigam[***] (2000)	OR		8.21	(3.61–18.6)				
			Sub-type specific						
			HBV only	6.84	(1.99–23.54)				

Ref #	Study (year)	Type of Estimator	Stratified by:	Unadjusted Estimate	95% CI	Stratified by:	Adjusted Estimate	95% CI	Adjustment factors:
			Cholestatic only	9.03	(3.36–24.2)				
15	El-Zayadi (1998)	OR		2.7	(1.7–4.4)				

OR, odds ratio; HR, hazard ratio, IRR, incidence rate ratio; dx, diagnosis; HAART, highly active anti-retroviral therapy; hx, history; MSM, male who has sex with males

* OLD, non-HCV related causes of chronic liver disease including alcohol-related, cholestatitic, hepatitis B, etc.

** DM risk-*a priori* specified DM risk category, high risk=yes if (age>60 or BMI>34.9 or family hx) *or* (age 50–59 & BMI 30–34.9) *or* (age 55–59 & BMI 25–9.9), low risk=all non-high risk

*** Pre-transplant time period only.